# THE SYNTHESIS OF γ-PHENYL- α, α-DIMETHYL-n-BUTYROPHENONE: A PREPARATORY STUDY FOR A FREE RADICAL MECHANISM REACTION

A THESIS

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The writer wishes to thank Dr. K. A. Huggins for his thoughtfulness and generosity in helping to make this work possible. Especial thanks are due Dr. H. C. McBay, research adviser, who called attention to errors and suggested improvements, constructed special pieces of apparatus, interpreted data and gave encouragement. From his helpful criticism and his meticulous attention to detail the writer was imbued with the thought that chemistry, apart from being an embodiment of facts, consists of attitudes and well-planned methods for the interpretation of chemical phenomena.

The financial assistance received from the National Science Foundation through its institute and fellowship programs made this work possible. This assistance is gratefully appreciated.

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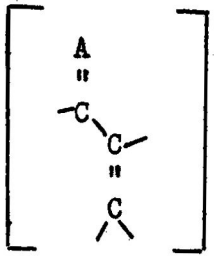
## THEORETICAL

Recent work in the area of Free Radical Mechanisms indicates that phenyl ketones as well as quinones trap free radicals.[1-8] That the element of structure, suggested as follows,



(where A may be N, O, S, C, etc)

is common to radical traps and that benzoate esters may function as radical traps were proposed by McBay.[9] In addition to this structural hypothesis a mechanism is suggested for the reaction of acetophenone with the methyl free which involves the production of a transitory styrene oxide-type intermediate. It is further proposed that this intermediate reacts with the acetophenone in a chain reaction to produce polymers.[10]

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[1]M. S. Krarasch, H. C. McBay and W. H. Urry, J. Am. Chem. Soc., 70, 1269 (1948).

[2]M. Levy and M. Szwarc, J. Am. Chem. Soc., 77, 1949 (1955).

[3]M. Szwarc and J. Smid, J. Am. Chem. Soc., 78, 3322 (1956).

[4]M. Szwarc and A. Rembaum, J. Am. Chem. Soc., 77, 4468 (1955)

[5]L. F. Fieser and A. E. Oxford, J. Am. Chem. Soc., 64, 2060 (1942).

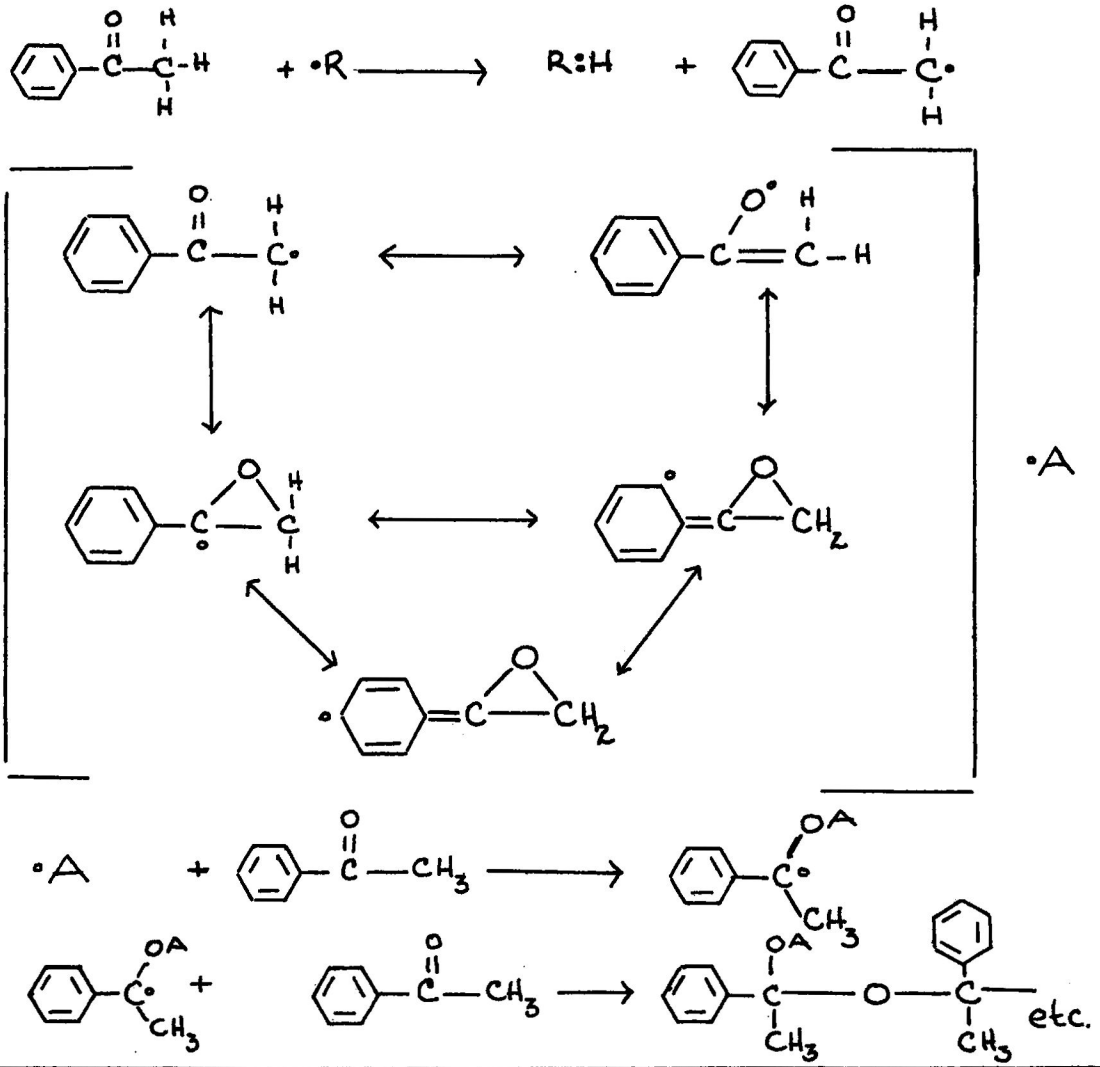
[6]von H. Weiland and A. Meyer, Ann., 551, 249 (1942).

[7]G. S. Hammond, J. T. Rudsell and F. J. Modic, J. Am. Chem. Soc., 78, 4914 (1956).

[8]R. A. Benkeser and R. B. Gosnell, J. Am. Chem. Soc., 78, 4914 (1956).

[9]S. M. McBay, "Free Radical Mechanisms: The Radical trapping Ability of some Phenyl Ketones and Benzoate Esters", Unpublished Master's Thesis, Department of Chemistry, Atlanta University, 1957, pp. 24-26.

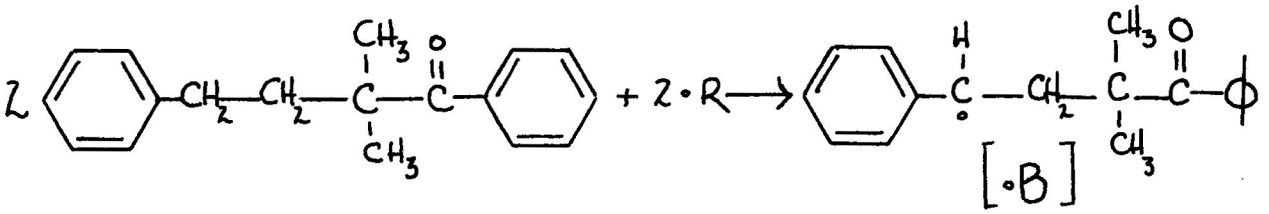
Green[11] sought evidence for or against the hypothesis of the styrene oxide-type intermediate and further attempted to test this hypothesis through ultraviolet photolysis of acetophenone and of styrene oxide. The radical trapping ability of phenyl ketones and the formation of a transitory styrene oxide-type intermediate is represented as follows:

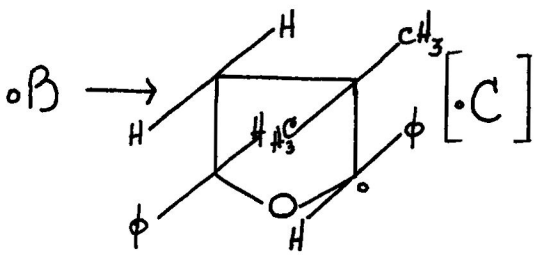


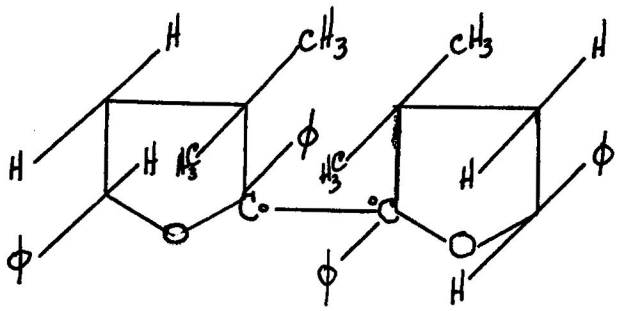
[10] Ibid.

[11] F. Green, "A Comparative study of the Ultraviolet Photolysis of Acetophenone and Styrene Oxide: The Question of a Non-Classical Free Radical Intermediate", Master's thesis in preparation, Department of Chemistry, Atlanta University.

To further the study in Free Radical Mechanisms this worker proposed a synthesis of a diaryl alkyl ketone with a benzoyl group attached at a distance from the site of free radical attack which is optimum for ring formation. If such a molecule were subjected to the hydrogen abstractinn of methyl free radicals produced by the thermal decomposition of diacetyl-peroxide or other sources of free radicals, such as diethylperoxidicarbonate and ditertiarybutylperoxide, one would expect to observe assistance from afar through cyclizatinn by a ketophenyl group resulting in the formatinn of hydrofurance and pyrane-type compounds. This proposed reaction is represented as follows:







Meso and Racemic

It is plausible that (•A ) is stabilized by resonance as indicated and this suggest that the intermediate (•C ) might dimerize as indicated in the above reaction for the same reason. The alpha carbon to the one bearing the unshared electron must have an hydrogen atom for disproportionation to occur. The gem-dimethyl groups in the molecule are expected to prevent the disproportionation. The isolation and characterization of such cyclic or dimeric hydrofuranes or pyranes would be inderect evidence for the occurrence of intramolecular radical trapping enhanced by neighboring group, ketophenyl, participation.

The purpose of this study was to develop feasible synthetic routes for the preparation of γ-phenyl-α,α-dimethylbutyrophenone. The compound, α, α-dimethylsuccinic acid, needed for the initial reaction was not commercially available; consequently three different procedures were used to determine the one best suited for synthetic work. These were as follows:

(1) Hydrolysis of the dinitrile, α,α-dimethylsuccinodinitrile,

(2) Permanganate oxidation of the cyclic diketone, dimethyldihydroresorcinol (5,5-dimethyl-1,3-cyclohexanedione),

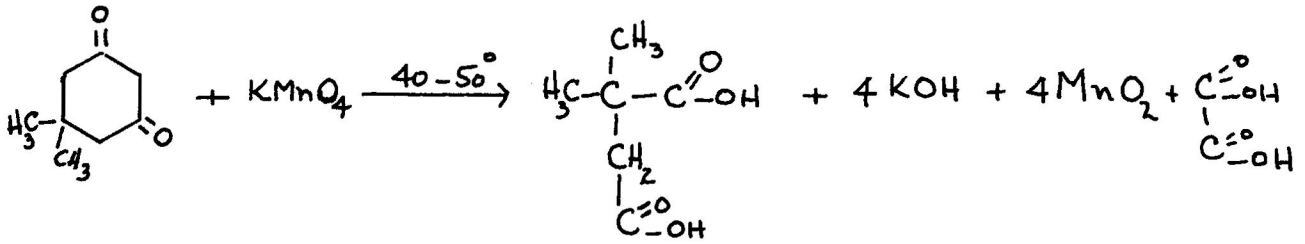
(3) Condensation of ethyl sodio-cyanoacetate with acetone cyanohydrin and subsequent degradative hydrolysis of the condensate.

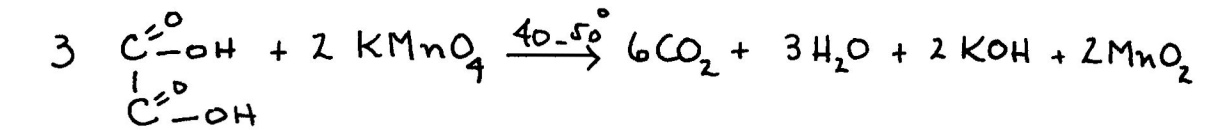
Distillation at reduced pressure or refluxing the initial acid, α,α-dimethylsuccinic acid, with acetyl chloride converted it to its anhydride. A Friedel-Crafts succinoylation of benzene with this anhydride lead to the formation of the keto acid, β-benzoyl-α,α-dimethylpropionic acid. The Clemmensen reduction and the Wolff-Kishner reduction were used to selectively reduce the keto group in the keto acid. The acid, γ-phenyl-α,α-dimethyl-n-butyric acid (β-benzyl- α, α-dimethylpropionic acid) resulting

from the selective reduction of the keto acid would have the desired characteristics to produce the proposed diaryl alkyl ketone as previously described.

The conversion of γ-phenyl- α, α -dimethyl-n-butyryl chloride, and subsequent treatment of the acid chloride with the proper organo-metallic reagent lead to the formation of the ketone, γ-phenyl- α, α -dimethyl-n-butyrophenone. Alternate routes were either taken or considered throughout the entire work. These and the total reaction scheme are outlined below:

1. α, α-Dimethylsuccinic acid.





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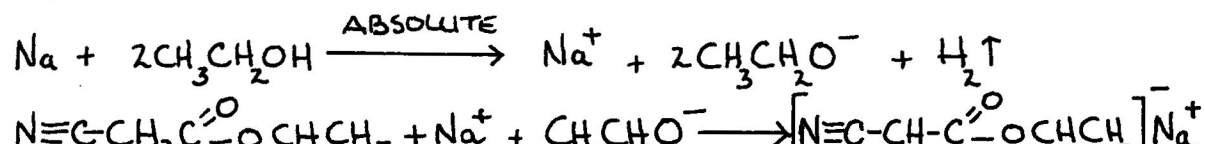
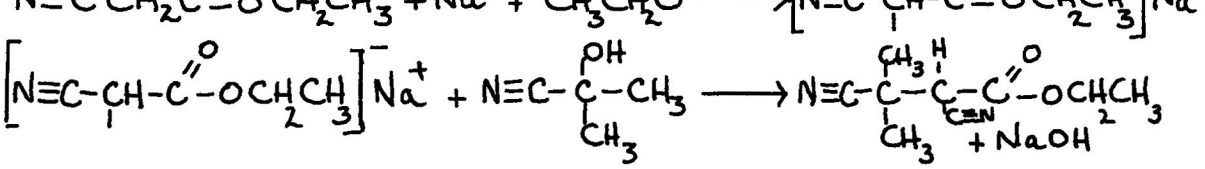
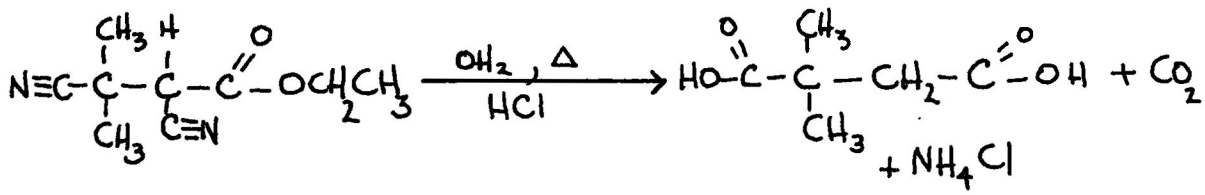
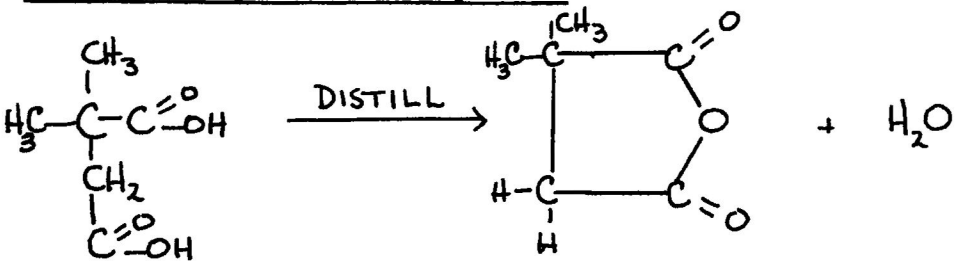


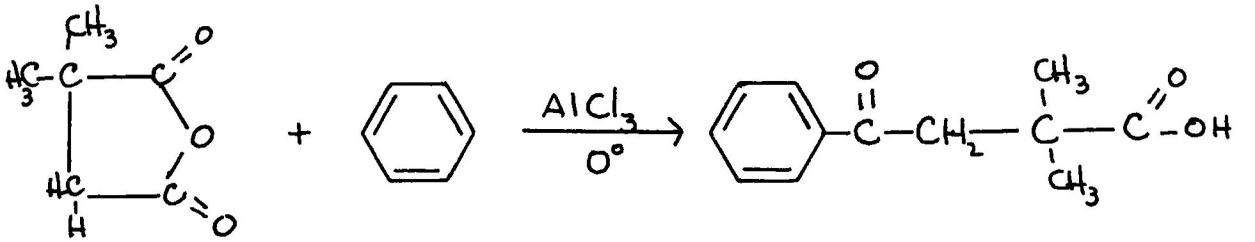




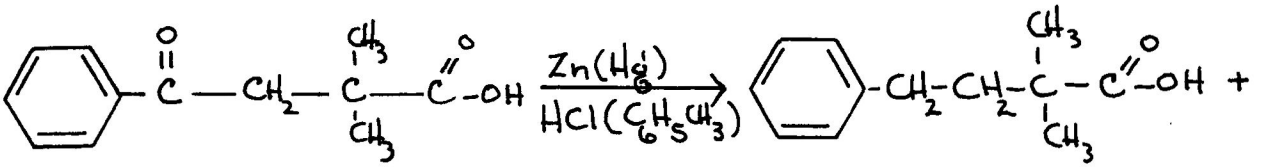
2. <u>α, α-Dimethylsuccinic anhydride.</u>



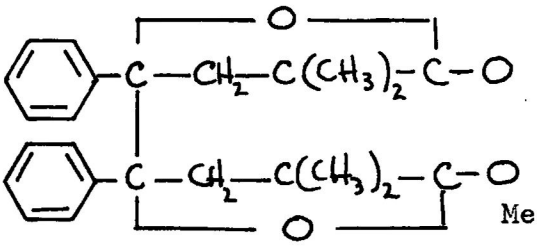

3. <u>β-Benzoyl- α, α-dimethylpropionic acid.</u>




4. <u>β-Benzyl- α, α-dimethylpropionic acid (γ-phenyl- α, α-dimethyl-n-butyric acid).</u>

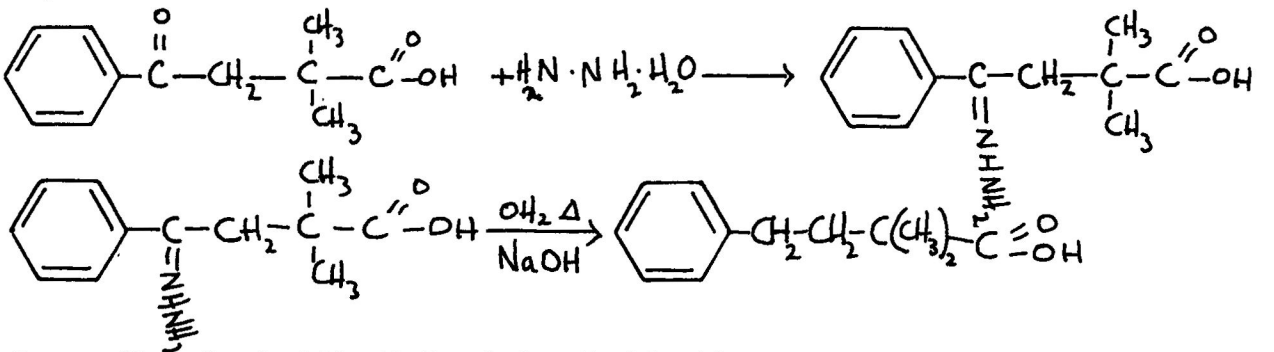



By-product of the reduction.

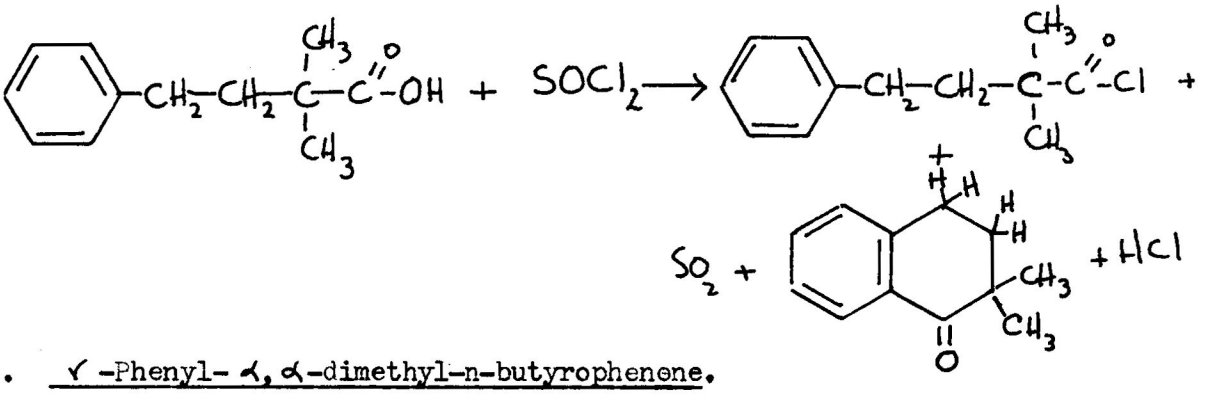


Meso and Racemic

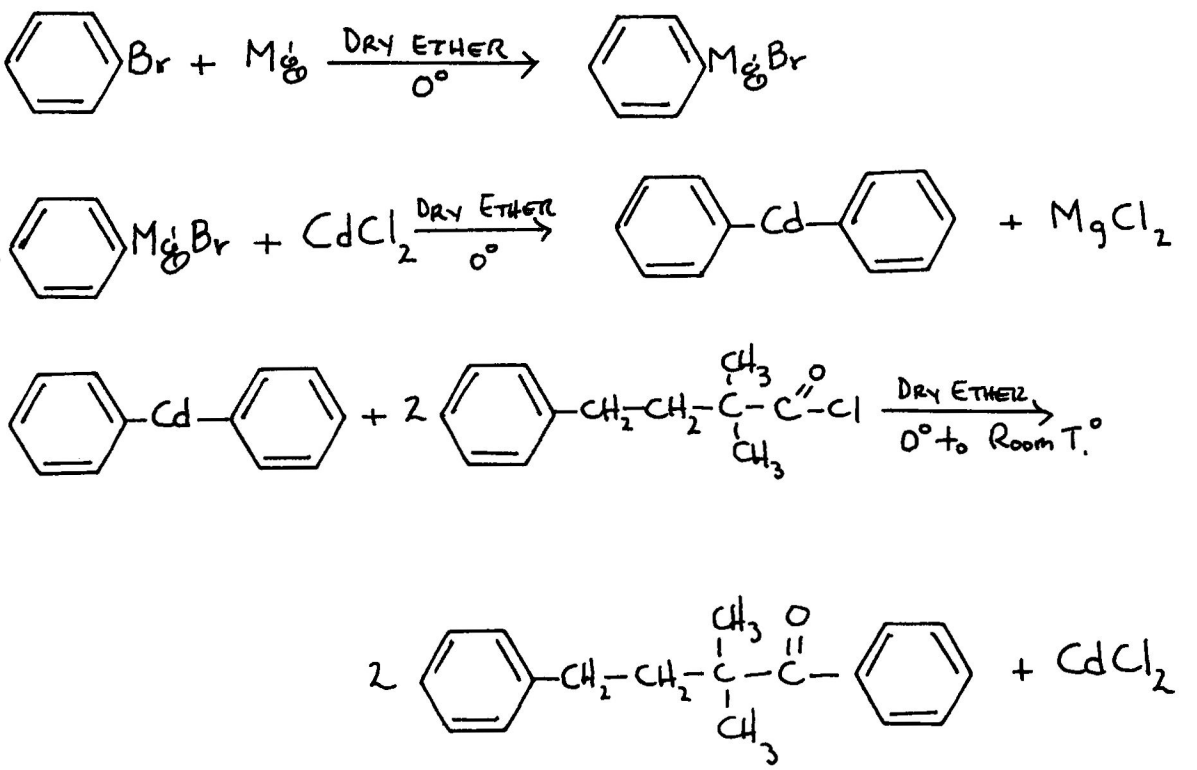
or,



5. γ-Phenyl-α,α-dimethyl-n-butyryl chloride.



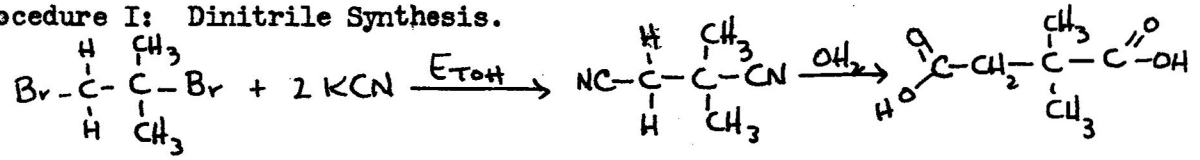
6. γ-Phenyl-α,α-dimethyl-n-butyrophenone.



The difficulties encountered in the syntheses described above were many.

The Preparation of $\alpha,\alpha$-Dimethylsuccinic Acid.

Procedure I: Dinitrile Synthesis.



This reaction proceeds with the application of heat or without at room temperature. Yet, in either case the yields are insignificant as was found by Hell and Rothberg.[12] Improvements in reaction conditions such as an increase in reaction time at room temperature and direct hydrolysis of the dinitrile without isolation were found not to increase the yields in two different runs.

Procedure II: The Permanganate Oxidation of 5,5-Dimethyl-1,3-cyclohexanedione.[13] This reaction (See equations p. 5, this thesis) had the decided advantage of giving better yields but the disadvantage of using small quantities of starting compounds in very large volumes of basic solution of permanganate. To overcome this difficulty in an attempt to stock-pile the $\alpha,\alpha$-dimethylsuccinic acid and to work with larger quantities of starting material, larger reaction vessels (12 liters) were used. Using these vessels the quantities of starting material could only be doubled. 2-Butanone was substituted as a solvent for the extraction of the acid instead of ethyl acetate which hydrolyzes to acetic acid, and a continuous extractor of five (5) liter capacity was employed for the operation. The use of the continuous extractor accounts for the increase in yield.

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[12] C. Hell and M. Rothberg, B., 22, 1740 (1889).

[13] D. Vorlander and S. Gartner, Ann., 304, 15 (1899).

Procedure III: The condensation of Ethyl sodio-cyanoacetate with Acetone cyanohydrin.[14] This approach (See equation, p. 5, this thesis.) gave excellent results as compared to the other two methods for the preparation of the $\alpha,\alpha$-dimethylsuccinic acid.

The conversion of $\alpha,\alpha$-dimethylsuccinic acid to its anhydride by distillation[15] proved superior to dehydration with acetyl chloride.[16]

The Friedel-Crafts succinoylation or condensation of $\alpha,\alpha$-dimethylsuccinic anhydride with benzene gave good yields of the keto acid, $\beta$-benzoyl-$\alpha,\alpha$-dimethylpropionic acid.[17-19] The Clemmensen reduction was used for the selective reduction of the keto acid.[20-22] Three products were isolated:

1) the reduced acid, $\gamma$-phenyl-$\alpha,\alpha$-dimethyl-n-butyric acid,

2) a high-melting (264°) lactone, $\gamma,\gamma'$-diphenyl-$\alpha,\alpha,\alpha',\alpha'$-tetra methyl-$\gamma,\gamma'$-suberodilactone,

3) a lower-melting (70-71°) waxy form of a lactone which from all indications was an isomeric form of (2).

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[14] A. Higson and J. F. Thorpe, J. Chem. Soc., 89, 1455 (1906).

[15] S. Levy and P. Englander, Ann., 242, 201 (1887).

[16] A. Higson and J. F. Thorpe, op. cit.

[17] E. Rothstein and M. A. Saboor, J. Chem. Soc., 425 (1943).

[18] G. R. Clemo and H. G. Dickinson, J. Chem. Soc., 255 (1937).

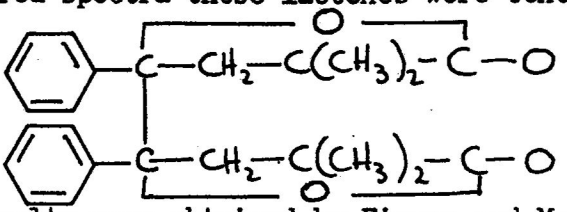
[19] M. A. Saboor, J. Chem. Soc., 922 (1945).

[20] E. L. Martin, J. Am. Chem. Soc., 58, 1438 (1936).

[21] R. F. Cox and R. T. Stormont, "Organic Synthesis", Col. Vol. II, New York: John Wiley and Sons, Inc., 1943, p. 499.

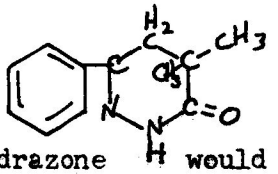
G. R. Clemo, R. D. Haworth and E. Walton, J. Chem. Soc., 2381 (1929).

On the basis of qualitative tests, carbon-hydrogen analysis, isomer number and infrared spectra these lactones were tentatively assigned the structure:



Similar results were obtained by Fieser and Martin[23] during the Clemmensen reduction of γ-phenyl-n-butyric acid.

An alternate procedure, the Huang-Minlon improved Wolff-Kishner reaction,[24] was also used to reduce the keto acid. Despite the use of the improved procedure the yield of the reduced acid was insignificant as compared to the yield from the Clemmensen reduction using the same quantities of starting materials. From the Huang-Minlon procedure was isolated, in addition to the small amount of reduced acid, a product which analyzes correctly for the cyclic derivative:



Such cyclization of the hydrazone would understandably inhibit the Wolff-Kishner type reaction as described by Huang-Minlon, and it is the opinion of the writer that this might very well account for the failure of that technique to reduce in good yield this particular acid.

The conversion of γ-phenyl-α,α-dimethyl-n-butyric acid to the acid chloride, γ-phenyl-α,α-dimethyl-n-butyryl chloride, was accomplished through reaction with thionyl chloride. Phosphrous pentachloride was used

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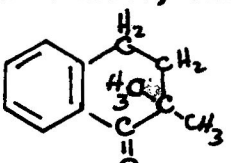
[23] L. F. Fieser and E. L. Martin, "Organic Synthesis", Vol. XV, New York: John Wiley & Sons, Inc., 1935, p. 64.

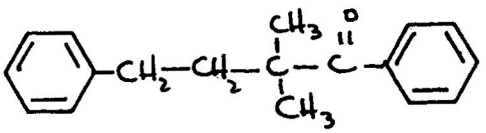
[24] Huang-Minlon, J. Am. Chem. Soc., 68, 2487 (1946).

also for this purpose, but it proved unsatisfactory. A heavy-viscous liquid resulted after distillation of the solvent, dry benzene. No attempts were made to isolate the acyl halide after removal of the thionyl chloride. Through a Grignard-type reaction the acyl halide was treated with diphenyl cadmium. Two products were isolated:

1) a fragrant, straw-colored, viscous oil, presumably,



2) a light, transparent, low-melting, parafin-like solid.



The yield of the oil was greater than that of the solid. While the solid reacted with 2,4 -dinitrophenylhydrazine the oil did not. It is possible that thionyl chloride and phosphorous pentachloride, like aluminum chloride, as Fieser[25] points out, might lead to the formation of a cyclic ketone by intramolecular cyclization between an aromatic ring and an acid chloride group in the side chain. This might account for the low yield of the desired non-cyclic ketone in comparison to the amount of oil isolated from the reaction mixture. Moreover, Brown and Greenberg[26] found that a Friedel-Crafts acylation of benzene with 3,3 -dimethylglutaryl chloride leads to the formation of $\beta$, $\beta$ -dimethyl- $\delta$, $\delta$ -diphenyl- $\delta$-valerolactone instead of the desired ketone. Although the conversion of the acid chloride, $\gamma$-phenyl- $\alpha$, $\alpha$-dimethyl-n-butyryl chloride, to the corresponding phenyl ketone is not strictly analogous to the

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[25] L. F. Fieser and M. Fieser, Advanced Organic Chemistry, New York: Rheinhold Publishing Corp., 1961, p. 658.

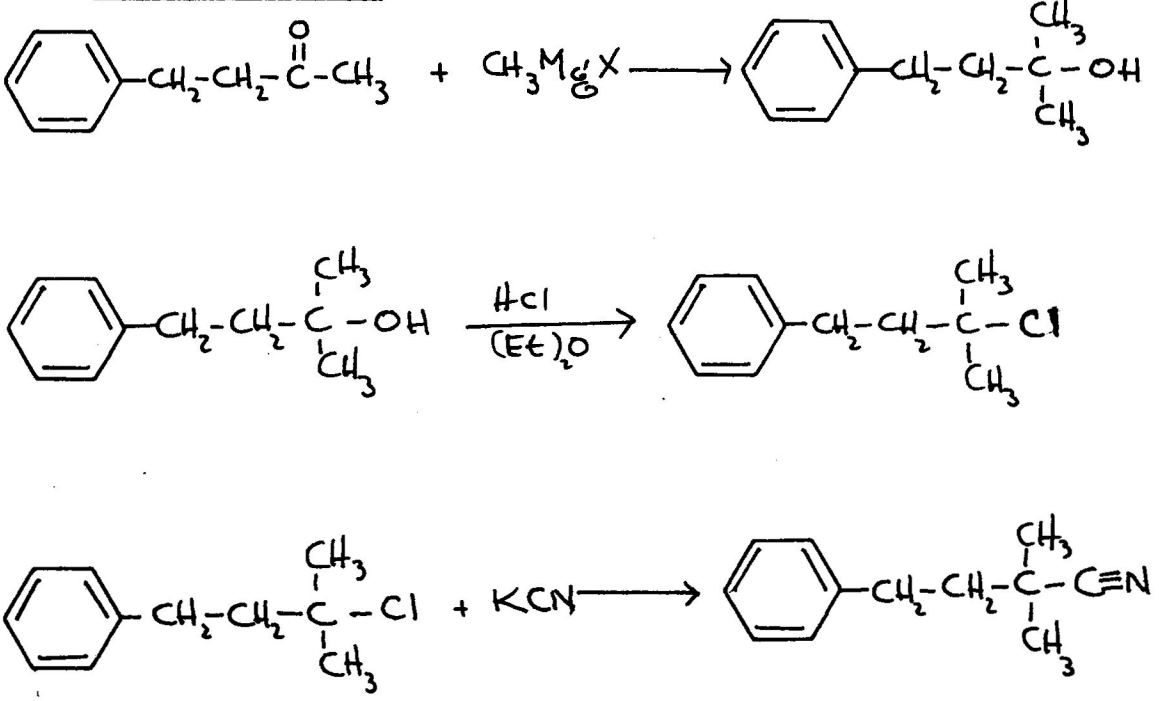
[26] W. G. Brown and F. Greenberg, J. Org. Chem. 28, 599 (1963).

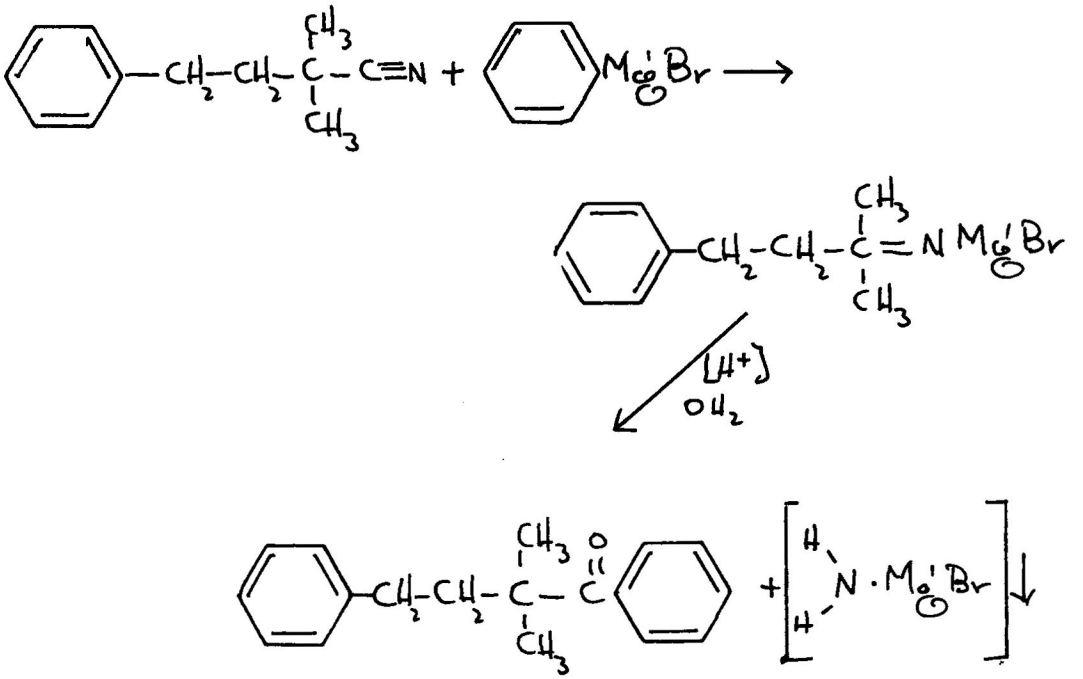
case of Brown and Greenberg, who sought to convert a delta keto acid to a phenyl ketone via Friedel-Crafts acylation of benzene, this procedure was avoided for the reason reported. Nevertheless, difficulties arose with the use of highly acid media in the conversion of the acid to the acid chloride. (See equation, p. 7, this thesis.)

Spectroscopic data for some of the compounds and chemical evidence for all compounds isolated from the various reactions in this synthesis are given in the experimental part.

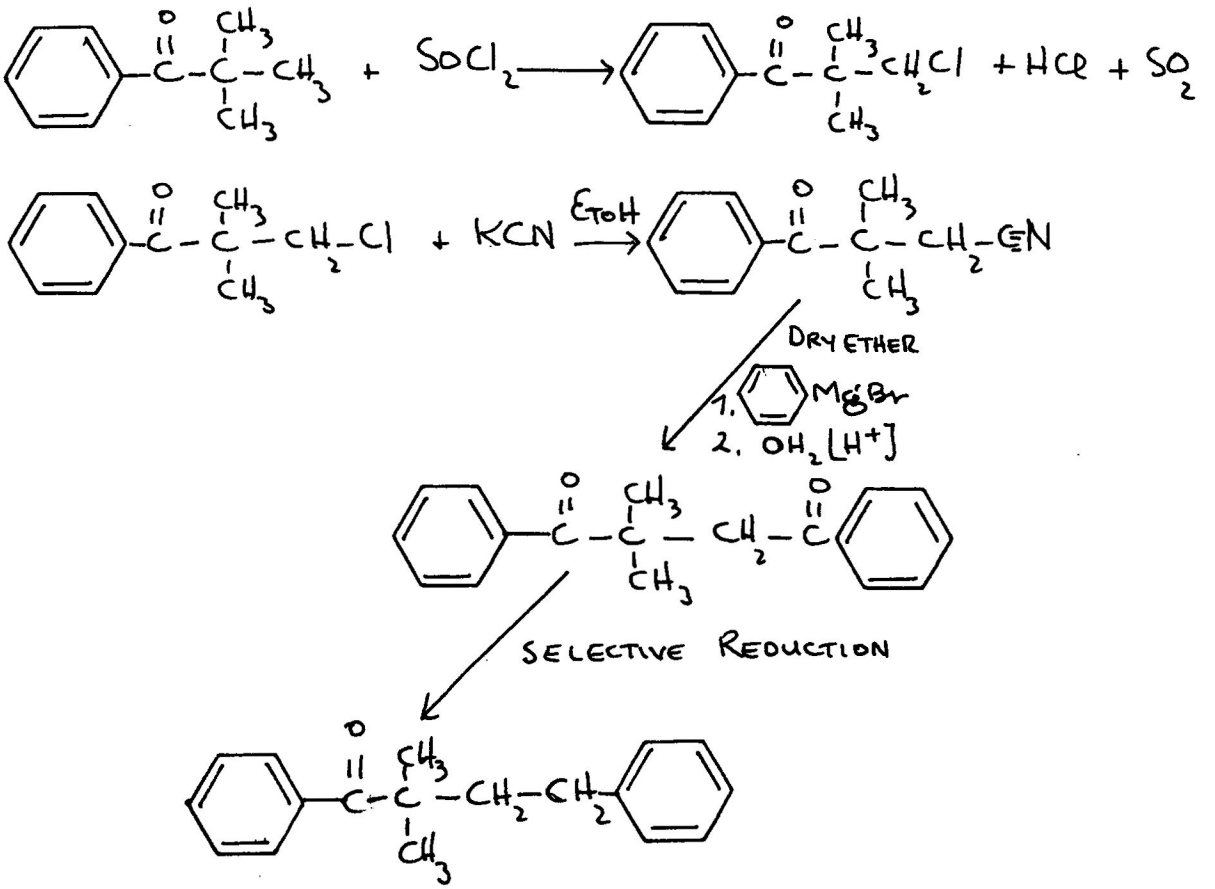
Clearly, the reaction scheme outlined in this study gave unsatisfactory results in the synthesis in quantity of γ-phenyl- α, α-dimethyl-n-butyrophenone. Other possible synthetic routes are suggested for future study:

Suggested Scheme I.





Suggested Scheme II.



## Experimental*

### The Preparation of $\alpha, \alpha$-Dimethylsuccinic acid.

#### Procedure I[27]

Two, (1) & (2), 3-neck, 2 liter flasks equipped with a reflux condenser, dropping funnel and a mercury seal with a mechanical stirrer containing 250 g of potassium cyanide in aqueous ethanol (2:1) were: (1) heated for eight hours at 75-80° and (2) allowed to stand at room temperature for two weeks. The ethanol was distilled off and the residue containing the 2,2-dimethylbutyldinitrile was extracted with ether and dried over calcium chloride. The ether was removed and the residual oil acidified with hydrochloric acid. The resulting white crystalline solid after recrystallization from hot water melts at 137-138°. Reported m. p. 139°. Yield: 0.20 g.

Notes.- 1. Distillation decomposes the dinitrile. The ethanol should be distilled off and the residue hydrolyzed by acid. Attempts to distill the dinitrile after removal of the solvent gave a wide fluctuation of temperature: 80-105° at the water pump and 92-98° at reduced pressure (1 mm). Hence, distillation was discontinued.

2. Reported b. p. of 2,2-dimethylbutyldinitrile 218-220°. Observed b. p. 216-217°. The dinitrile is highly soluble in water.

3. An extremely copious precipitate of inorganic salt results as the reaction proceeds either on heating or standing at room temperature. On heating, the reaction mixture gets noticeably dark brown after two or three hours of heating. At room temperature the reaction mixture is lighter in color.

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*Analyst: Clark Microanalytical Laboratory, 104½ West Main Street, Urbana, Illinois.

[27]C. Hell and M. Rothberg, op. cit.

Procedure II[28]

To 10 g of 5,5-dimethyl-1,3-cyclohexanedione and 30 g of sodium carbonate in one liter of water was added 52 g of potassium permanganate in 3.5 l of water. The reaction mixture was kept at 40-50°. Manganese dioxide precipitates as the reaction proceeds and the mixture becomes clear on completion of the reaction. After filtration, the basic aqueous solution was acidified with hydrochloric acid and extracted with ethyl methyl ketone (2-butanone) using a continuous extractor. The solvent was removed on a fractionating column and the residue distilled at reduced pressure. A small quantity of the suspected anhydride was hydrolyzed with water to the acid. M. p. 137-138°. Reported m. p. 138-139°.

Notes.- 1. Distillation was resorted to in order to make a direct conversion of the acid to its anhydride and to avoid contamination of the final product with a brown material which came out during the extraction.

2. 2-Butanone was substituted for ethyl acetate as the extracting solvent. Ether was totally unsatisfactory. 2-Butanone had the advantage increasing the quantity of acid extracted but the disadvantage of extracting some of the inorganic salts with the acid.

3. Since small quantities of starting compounds required large volumes of aqueous basic permanganate this procedure was completed in several separate runs in order to stock-pile the acid.

Procedure III[29]

Sodium (27.5 g; theoretical required 29.0 g) was dissolved in 350 g of

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[28] D. Vorlander and S. Gartner, op. cit.

[29] A. Higson and J. F. Thorpe, loc. cit.

absolute ethanol in a pre-dried reaction vessel equipped with a mechanical stirrer, thermometer well, dropping funnel and a mercury seal. Ethyl cyanoacetate (420 g) was added slowly. This suspension was allowed to cool and to it was added 110 g of acetone cyanohydrin in an equal volume of ethanol. An increase in temperature was noted. The contents of the flask were left to stand approximately three hours with stirring . On completion of the reaction the contents of the flask were semi-solid. An excess of water was added and the solution made faintly acid with hydrochloric acid. Extraction with ether followed. The ether extract was washed with water and dilute sodium carbonate solution and subsequently dried over sodium sulfate. Removal of the ether was accomplished on the steam bath. The residual oil was distilled at reduced pressure giving a colorless, mobile liquid (ethyl- , dicyano- , -dimethyl-propionate). B. p. 147.1° at 20 mm. Reported b. p. 150° at 22 mm.

Hydrolysis.- To this colorless liquid was added four times its volume of concentrated hydrochloric acid. The reaction mixture was refluxed vigorously for 3-4 hours. After hydrolysis was complete and on cooling a large quantity of crystalline material precipitated. Recrystallization of this crystalline material gave a white solid melting at 139°. Reported m. p. 139°. Yield: 92.8 g.

Acetone Cyanohydrin.-Required in this condensation was acetone cyanohydrin. This compound was prepared by a procedure as outlined in "Organic Synthesis".[30] The observed b. p. of the final product during two runs was

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[30] R. F. Cox and R. T. Formart, "Organic Synthesis", Col. Vol. II, New York: John Wiley and Sons, Inc., 1943, pp. 7-8.

74.6-75.6° at 4 mm and 65-65.6° at 2 mm. Reported b. p. 78-82° at 15 mm. Yield: 1250 g.

The Conversion of $\alpha$-$\alpha$-Dimethylsuccinic acid to its anhydride.

Procedure I[31-34]

The $\alpha$, $\alpha$-dimethylsuccinic acid as prepared above in procedures II and III was distilled under reduced pressure with heating. The boiling points of the anhydride at the water pump in three successive distillations were: 98-108°, 104-109° and 108-109°. B. p. with the oil pump: 72-74° at 2 mm. Reported b. p. (L. E.) 219-220°, b. p. 110° at 17 mm (V. H.), b. p. 117° at 22 mm (A.). Yield: 136 g. $n_D^{20}$ 1.4448.

Procedure II[35]

Refluxing $\alpha$, $\alpha$-dimethylsuccinic acid with acetyl chloride was a method of Higson and Thorpe.

Notes.- 1. The boiling temperatures given in Procedure I of this conversion were four different distillations over a long period of time. This is necessary to insure almost complete removal of the water and further to minimize reconversion of the anhydride to the acid. Care must be taken to keep the anhydride under anhydrous conditions.

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[31] S. Levy and P. Englander, Ann., op. cit.

[32] P. E. Verkade and R. Hartman, R., 52, 948 (1933).

[33] von K. Auwer, Ann,, 292, 185 (1896).

[34] von Ferd. Barnstein, Ann., 242 139 (1887).

[35] A. Higson and J. F. Thorpe, loc. cit.

2. Refluxing the acid with acetyl chloride resulted in a second product in addition to the anhydride. The other product was a high melting, water soluble solid. Attempts to hydrolyze it to the acid failed.

The Preparation of β-Benzoyl- α, α-dimethylpropionic acid.[36-39]

One hundred thirty six grams (136 g) of α,α-Dimethylsuccinic anhydride in dry benzene was slowly added in five different runs to powdered Aluminum Chloride in dry benzene. The reaction rate was controlled by cooling. The mixture in each case was allowed to stand for 1-2 hours in order to come to room temperature. Completion of the reaction was by heating on a steam bath. The reaction mixture was poured into ice cold 5% Hydrochloric acid. The excess benzene was removed on a water bath under reduced pressure. Whencold the precipitated solid was filtered. Recrystallization was from hot 50% Ethanol. M. p. 168-169°. Reported m. p. 173°. Yield: 46.6 g.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88%; H, 6.84%.

Found: C, 69.87%; H, 6.96%.

Neutralization Equivalent: Calcd. for: 206.

Found 193.

Derivative.- 6-keto-3-phenyl-5,5-dimethyltetrahydropyridazine. The keto acid was heatedwith one half its weight of hydrazine hydrate on a water bath for 1 hour. When cool a white crystalline solid precipitated. M. p.

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[36] E. Rothstein and M. A. Saboor, op. cit.

[37] G. R. Clemo and H. G. Dickenson, op. cit.

[38] M. A. Saboor, J. Chem. Soc., op. cit.

[39] E. Berliner,"Organic Reactions", Vol. V., New York: John Wiley & Sons, 1949, pp. 229-245.

164-165°. Reported m. p. 167-168°.

Anal. Calcd. for $C_{12}H_{15}ON_2$: N, 13.80%

Found: N, 13.21%

Notes.- 1. Coarser or small lump aluminum chloride tends to give better yields than the finely powdered compound.

2. The reported 2,4-dinitrophenylhydrazone derivative of the keto acid melting at 198-199° was never isolated. The compounds isolated gave analyses different from the expected. Possibly, cyclization similar to that in the above derivative occurs.

The Preparation of β-Benzyl- α, α-dimethylpropionic acid ( γ-Phenyl- α,α-dimethylbutyric acid)

Procedure I[40-44]

Clemmensen Reduction. The zinc amalgam was prepared as follows: 120 g of mossy zinc, 12 g of mercuric chloride, 200 ml of water and 5-6 ml of conc. hydrochloric acid were shaken in a 1 liter flask for five minutes. This solution was decanted from the precipitated amalgam. The following reagents were added to the amalgam in the order as listed: 75 ml of water, 175

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[40] L. F. Fieser and E. L. Martin, "Organic Synthesis", Vol. XV, New York: John Wiley and Sons, Inc. 1935, p. 64.

[41] Adapted from: E. L. Martin, Organic Synthesis", Col. Vol. II, New York: John Wiley and Sons, Inc., 1943, p. 499.

[42] E. L. Martin, J. Am. Chem. Soc., op. cit.

[43] G. R. Clemo, R. D. Haworth, E. Walton, J. Chem. Soc., 2387 (1935).

[44] E. L. Martin, "Organic Reactions", Vol. I, New York: John Wiley and Sons, Inc., 1942, pp. 159-161.

ml of conc. hydrochloric acid, 100 ml of toluene and 50 g of the keto acid. The reaction mixture was refluxed 30 hours with the addition of 25 ml of conc. hydrochloric acid at 6 hours intervals. The reaction mixture was allowed to cool followed by the separation of the aqueous and toluene layers. The aqueous layer was diluted with water and extracted with three 100 ml portions of ether. The combined ether and toluene extract was washed and then dried over anhydrous sodium sulfate. From this etheral extract the ether was removed on a steam bath and the toluene under reduced pressure . Distillation was attempted but discontinued. (See notes). The residual material was added to hot water with the reduced acid separating out of solution. An insoluble portion of the residue gave on the addition of petroleum ether a waxy, low melting solid and a high melting crystalline solid. The three resulting products are characterized as follows:

Product I.- The reduced acid. M. p. 89-90°. Yield: 23.1 g

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.00%; H, 8.33%

Found: C, 75.08%; H, 7.14%

Product II.-The lactone, $\gamma, \gamma'$ diphenyl- $\alpha, \alpha, \alpha', \alpha'$, dimethyl- $\gamma, \gamma'$- suberodilactone. M. p. 264°. Yield: 4.1 g.

Anal. Calcd, for $C_{24}H_{26}O_4$: C, 76.19%; H, 7.18%

Found: C, 76.11%; H, 7.12%

Neutralization Equivalent: Calcd. for 378.

Found: 317 (See notes)

Product III. A suspected isomeric form of product II. M. p. 70-71°. Yield: 12.2 g

Notes.- 1. Distillation was discontinued because of charring and possible cyclization of the molecule.

2. Recrystallization or separation of the products was

better effected with hot water. Products II and III were insoluble in hot water. Petroleum ether effected the separation of products II and III.

3. Use of 100 ml of Toluene imiscible with the aqueous solution apparently impeded the formation of the polymolecular products.

4. The analyst had considerable difficulty in securing a saponification equivalent for product II; hence, the neutralization equivalent was found. Considerable hindrance in the molecule might also lead to difficulty in securing a more accurate neutralization equivalent.

Procedure II[45-46]

Wolff-Kishner Reduction.- Ten grams (10g) of keto acid, 5 g of sodium hydroxide, 80 ml of Triethyleneglycol and 5 ml of 85% Hydrazine hydrate were refluxed. After one hour the reflux condenser was removed until the temperature reached 195-200°. Refluxing was continued at that temperature for 3-4 hours. The reaction mixture was cooled, acidified and extracted with benzene. The benzene extract was washed with water and dried over Calcium chloride. Removal of the benzene left a solid residue which was recrystallized from 50% ethanol and subsequently hot water. M. p. 89-90°. Yield: Insignificant as compared to starting material.

Notes.-1. The reaction time was insufficient. The material had to be redissolved in solvent, more base added and refluxed for an additional 3-4 hours. Despite this the yield was not improved.

2. Analysis: As above.

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[45]Huang-Minlon, op. cit.

[46]David Todd, "Organic Reactions", Vol. IV, New York: John Wiley & Sons, Inc. 1948, p. 328.

The Conversion of β-Benzyl-α,α-dimethylpropionic acid to its Chloride, β-Benzyl-α,α-dimethylpropionyl chloride.

Procedure I[47]

β-Benzyl-α,α-dimethylpropionic acid (4 g) was refluxed with a slight excess of thionyl chloride (2.4 g) for 15 to 30 minutes. No attempt was made to isolate the product. The excess Thionyl chloride was distilled off by heating the reaction mixture on a water bath under reduced pressure. Ether was added and evaporated to remove the Thionyl chloride. Two runs were completed. The acyl halide in run 1 was taken up in dry benzene and the latter in anhydrous ether.

Notes.- 1. The reaction time should be limited to 15-30 minutes or less.

2. Prolonged heating and distillation of the final product will be avoided since possible cyclization of the molecule will result. A heavy, viscous material results.

3. Use of the acyl should be immediate in order to minimize loss of the acyl halide through possible cyclization.

Procedure II

Two grams of β-Benzyl-α,α-dimethylpropionic acid and 2 g of Phosphorous pentachloride in dry benzene were refluxed for 30 minutes. After removal of the benzene under reduced pressure a heavy viscous material remained in the reaction vessel.

Note: Phosphorous pentachloride apparently causes cyclization of the molecule.

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[47] W. J. Hickinbottom, Reactions of Organic Compounds, 3rd. ed., New York: Longmans, Green and Co., Inc., 1959, pp. 291-294.

The preparation of γ-Phenyl- α, α-dimethylbutyrophenone.[48]

Phenylmagnesiumbromide was prepared under anhydrous conditions using 16 g of Mono-bromobenzene and 2.4 g of magnesium in dry ether. The reaction was catalyzed with an iodine crystal. The reaction rate was controlled by cooling. Cadmium chloride (2.3 g) was added to the Phenylmagnesiumbromide to convert it to (4 g) Diphenyl cadmium. β-Benzyl- α, α-dimethylpropionyl-chloride in dry ether was slowly added to the cadmium Grignard reagent with stirring. The reaction vessel was allowed to come to room temperature. Decomposition was accomplished with 10% hydrochloric acid. The aqueous layer was separated and extracted with ether. The ether extract was washed with water and diluted sodium carbonate solution, and dried over anhydrous sodium sulfate. The ether was removed on a steam bath and the residue distilled under reduced pressure. Two fractions were collected: (1) a clear liquid which crystallized immediately in the receiver and (2) a heavy, colorless liquid. B. p. fraction (1) 80° at 2-3 mm. B. p. fraction (2) 145° at 2-3 mm and 182° at 4-5 mm. Yield: Fraction (1) 0.1 g. Fraction (2) 3.2 g.

Anal. Calcd. for $C_{18}H_{20}O$: C, 86.06%; H, 7.98%

Found: C, 86.28%; H, 7.23%

Spectral Analysis: Infrared Spectroscopy.[49-50]

Fig. 1 and 2: β-Benzoyl- α, α-dimethylpropionic acid.

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[48] Adapted from: David A. Shirley, "Organic Reactions", Vol. VIII, New York: John Wiley and Sons, Inc., 1954, pp. 35-37.

[49] A. D. Cross, Practical Infrared Spectroscopy, London: Butterworths, 1960, pp. 39-46.

[50] R. L. Shrimer, R. C. Fuson and D. Curtin, The Systematic Identification of Organic Compounds, 4th. ed., New York: John Wiley & Sons, Inc., 1959, pp. 167-179.

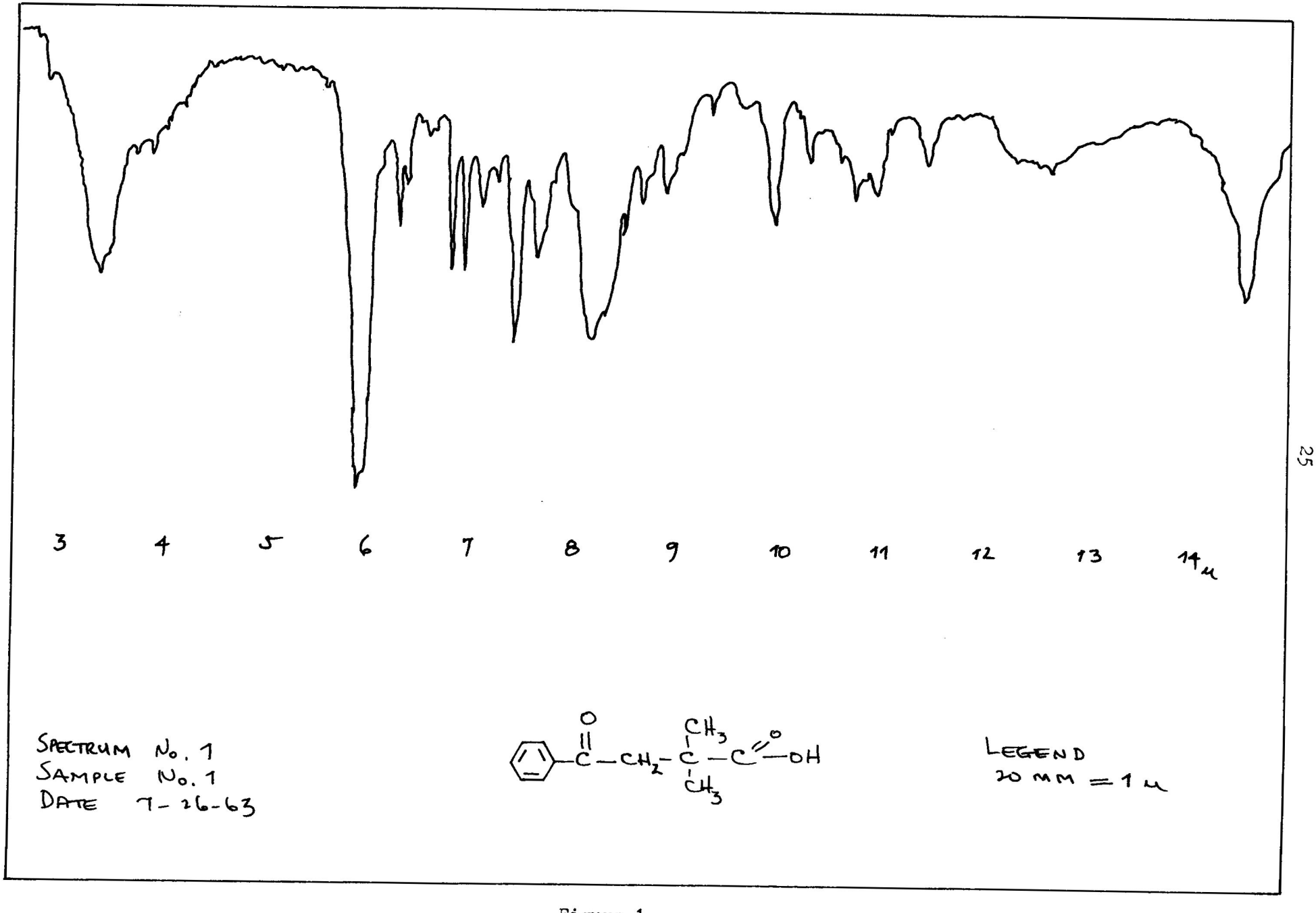
The infrared spectra for this acid shows carbonyl absorption bands at 5.80-5.90$\mu$, C=C bands at 6.35$\mu$, benzene substitution bands at 8.25$\mu$ and 14.51$\mu$. The OH vibration characteristic of carboxylic acids is seen at 3.30$\mu$. The carbonyl stretching vibration of carboxylic acids is more pronounced in Fig. 2 where a double band at 5.70-5.80$\mu$ indicates two carbonyl functions. Conjugation with the phenyl ring tends to lower the carbonyl frequency.

Figure 3: $\gamma$-Phenyl-$\alpha,\alpha$-dimethyl-n-butyric acid.

The OH and C=O stretching frequencies may be seen in this spectrum at 3.30$\mu$, 10.70$\mu$ and 5.85$\mu$ respectively. The position of the OH and C=O stretching frequencies in carboxylic acids are uncertain due to strong hydrogen bonding.

Figures 4 & 5: By-products of the Clemmensen Reduction Reaction.

The high and low melting forms of $\gamma,\gamma'$-diphenyl-$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-$\gamma,\gamma'$-suberodilactone show carbonyl absorption bands at 5.50-5.75$\mu$ (Fig. 4) and 5.55-5.79$\mu$ (Fig. 5). These bands are characteristic of gamma lactones.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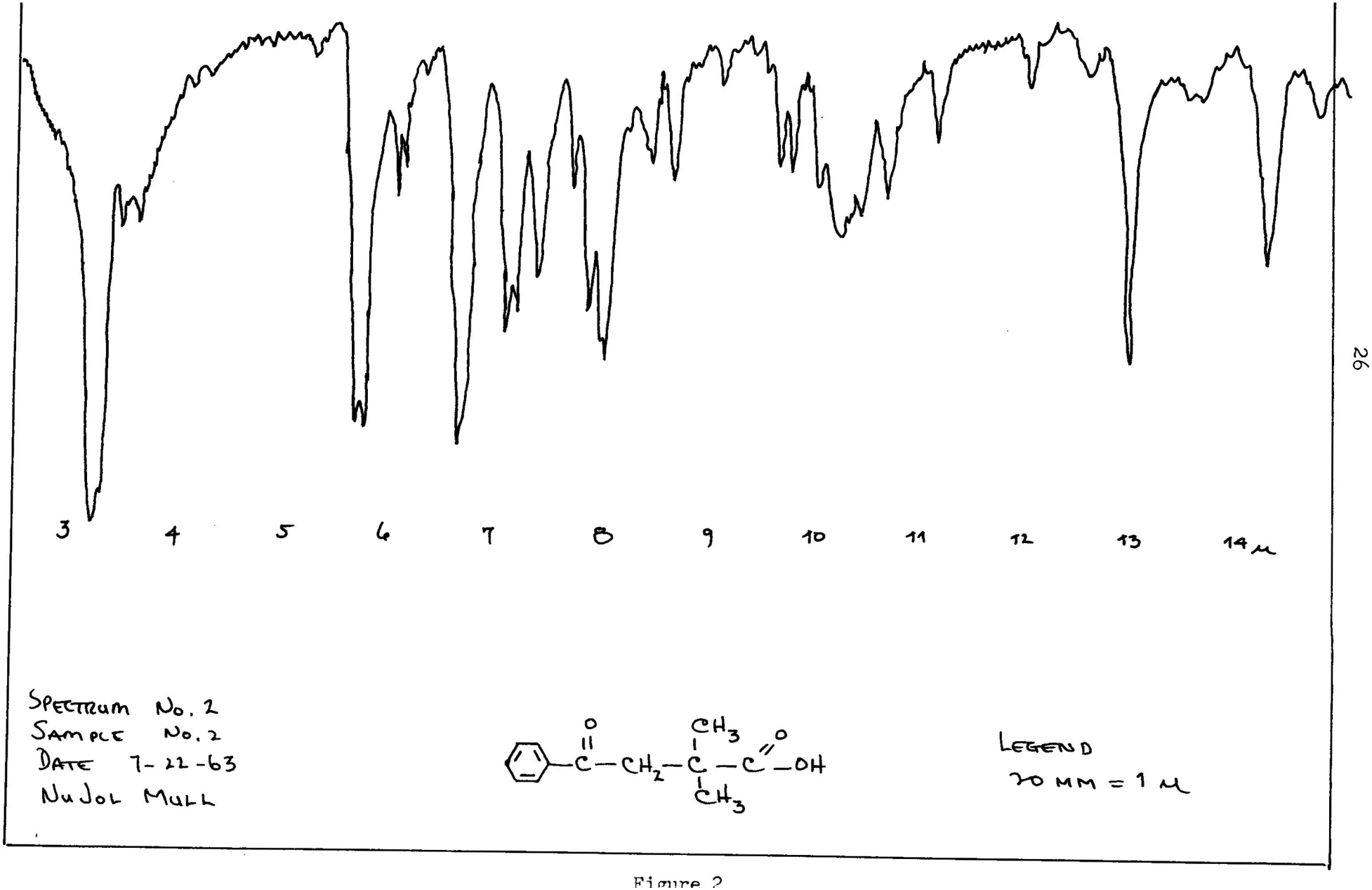
14 μ
SPECTRUM No. 1
SAMPLE No. 1
DATE 7-26-63
LEGEND
20 MM = 1 μ

Figure 1



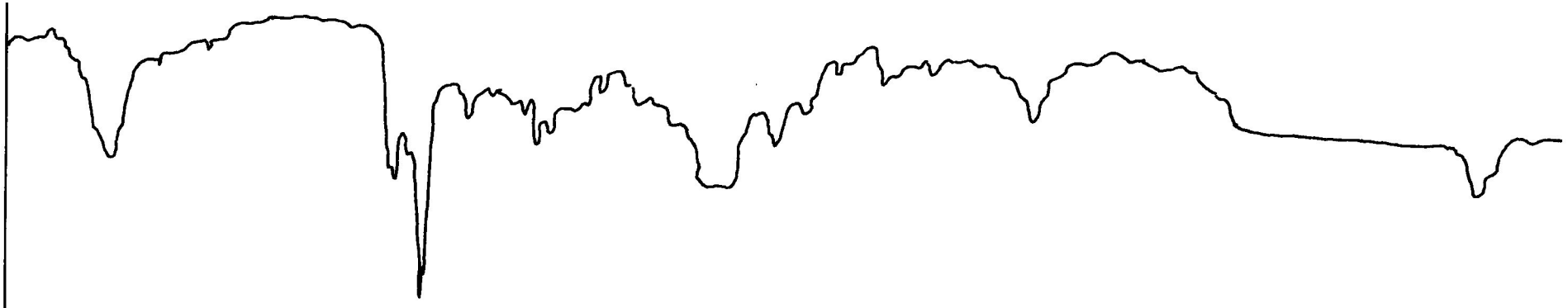

SPECTRUM No. 2
SAMPLE No. 2
DATE 7-22-63
NUJOL MULL



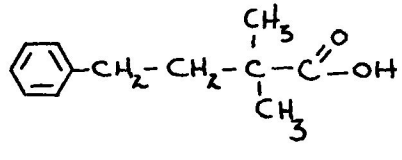
LEGEND
20 MM = 1 μ



Figure 2

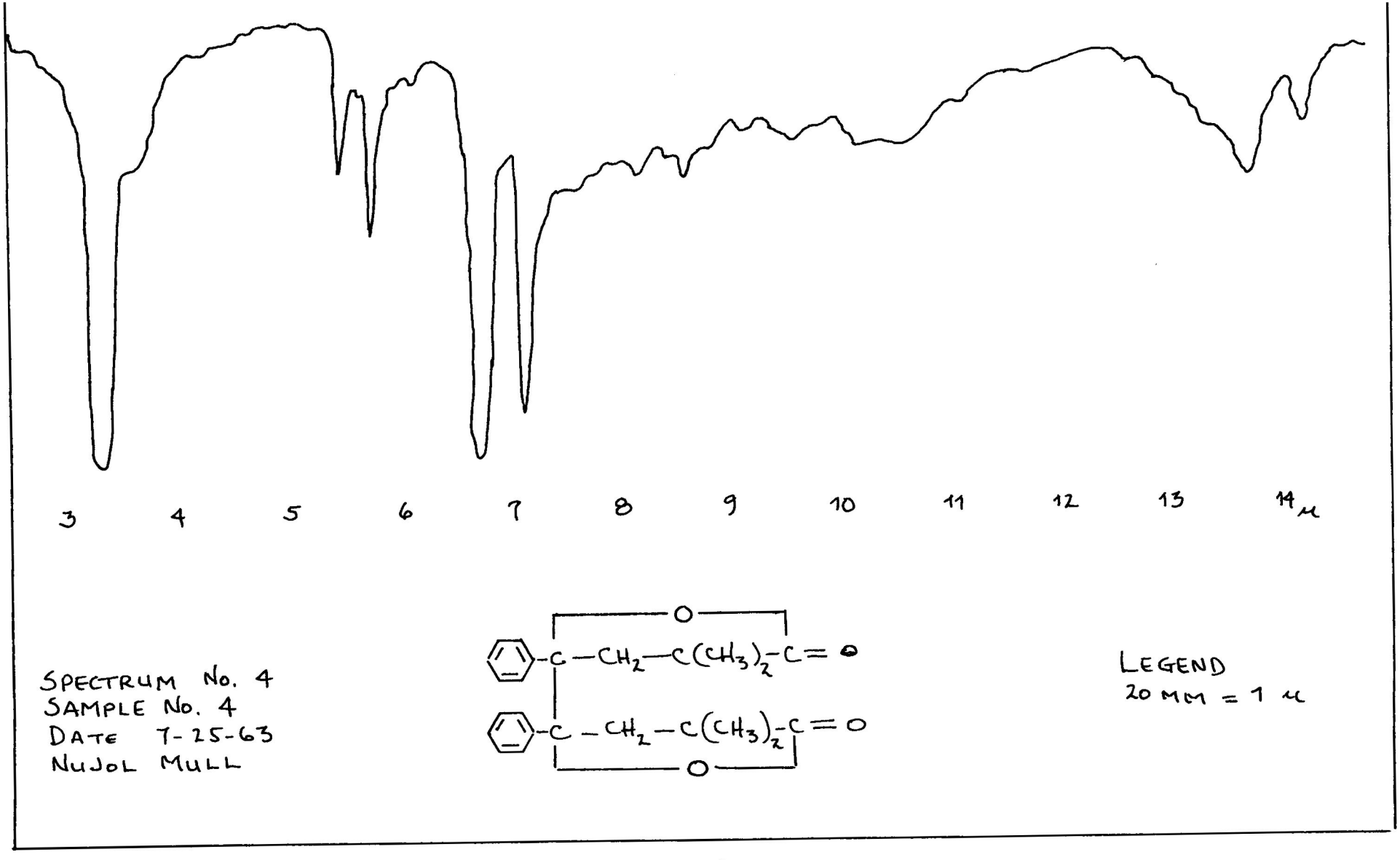



SPECTRUM NO. 3
SAMPLE NO. 3
DATE – 7-25-63
SOLVENT – CHLOROFORM



LEGEND
20MM = 1 μ

Figure 3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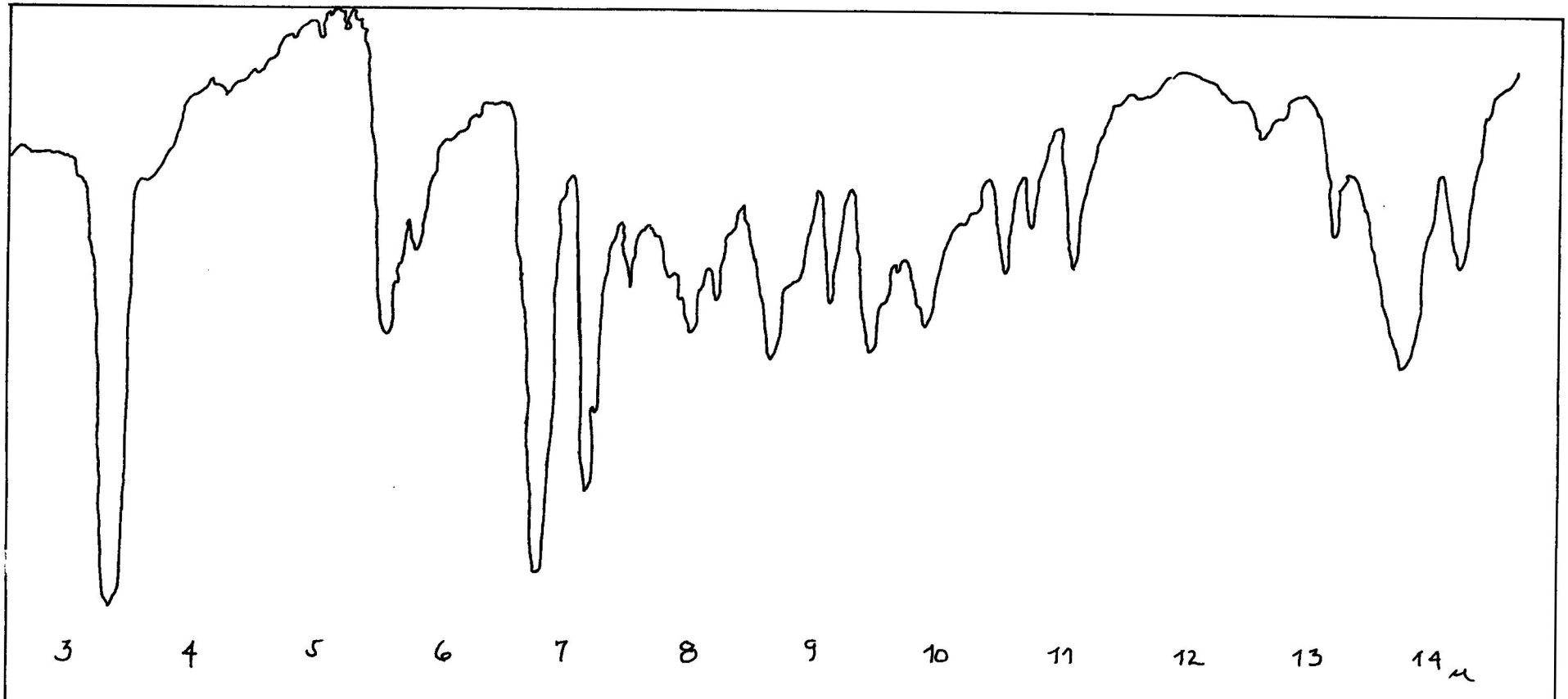
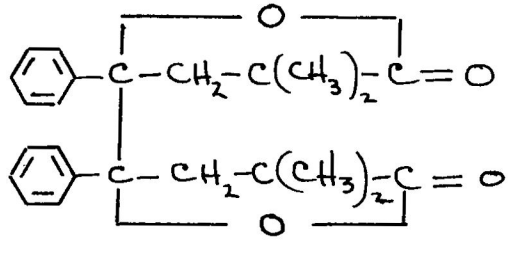
SPECTRUM No. 4
SAMPLE No. 4
DATE 7-25-63
NUJOL MULL
LEGEND
20 MM = 1 μ

Figure 4



SPECTRUM No. 5
SAMPLE No. 5
DATE - 7-25-63
NUJOL MULL

LEGEND
20 MM = 1 μ

Figure 5

## SUMMARY

The synthesis of the proposed diaryl alkyl ketone, γ-phenyl-α, α-dimethyl-n-butyrophenone, is described. The scope and limitations of this systhesis are included. Other possible synthetic routes are suggested. Spectral evidence for some of the compounds is listed.

The reaction scheme outlined in this study gave unsatisfactory results in the quantity of γ- phenyl-α, α-dimethyl-n-butyrophenone synthesized.

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